97. *The Preparation of 4 : 6-Dimethyl Altrose and 2 : 4 : 6-Trimethyl Altrose from Glucose.*

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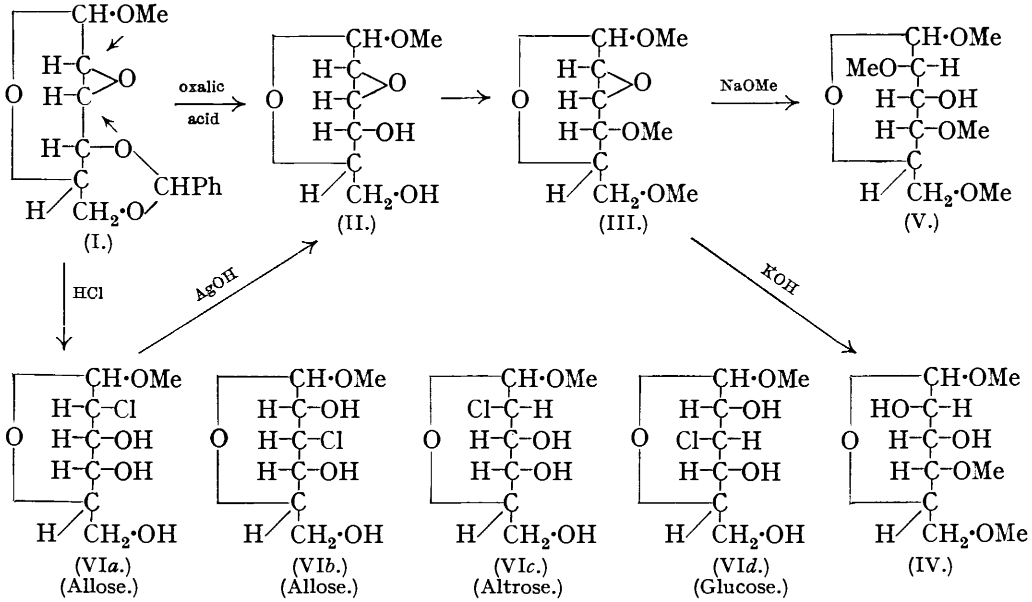
The starting point in this research was 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (I). Attempts to remove the benzylidene residue by hydrolysis with very dilute hydrochloric acid in acetone solution led to the production of two isomeric *α-methylhexoside chlorohydrins* to which no definite configuration may yet be ascribed. The removal of the benzylidene residue was ultimately achieved by means of hydrolysis with oxalic acid and the resulting 2 : 3-*anhydro-α-methylalloside* (II) was methylated to give 4 : 6-dimethyl 2 : 3-anhydro-α-methylalloside (III), which, in turn, yielded 4 : 6-*dimethyl α-methylaltroside* (IV) and 2 : 4 : 6-*trimethyl α-methylaltroside* (V) on treatment with aqueous caustic potash and a solution of sodium methoxide respectively.

Glucose was converted successively into 4 : 6-benzylidene α-methylglucoside (Irvine and Scott, J., 1913, **103**, 585; Freudenberg, *Ber.*, 1928, **61**, 1758), 2 : 3-di-*p*-toluenesulphonyl 4 : 6-benzylidene α-methylglucoside (Ohle and Spencker, *Ber.*, 1928, **61**, 2387; Mathers and Robertson, J., 1933, 696), and 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside (I) (Robertson and Griffith, J., 1935, 1196).



When substance (I) was treated with very dilute hydrochloric acid in acetone solution, it was expected that hydrolysis of the benzylidene residue would take place with the production of 2 : 3-*anhydro-α-methylalloside* (II). The reaction is more profound and, in addition to the removal of the benzylidene residue, the ethylene oxide ring is broken and an atom of chlorine enters the molecule. The product is a crystalline solid, m. p. 117—120°, which is not homogeneous, but from which two isomeric *α-methylhexoside chlorohydrins* have been separated in a pure condition by a tedious process of fractional crystallisation. The formation of a sugar chlorohydrin in the course of such a hydrolysis was first noticed by Müller (*Ber.*, 1934, **67**, 423). One of the new substances separates in small prisms, m. p. 160—162°, $[\alpha]_D^{15^\circ} + 113{\cdot}1^\circ$ in methyl alcohol, and the other in large prisms, m. p. 136—138°, $[\alpha]_D^{15^\circ} + 157{\cdot}2^\circ$ in methyl alcohol.

It is clear that the ethylene oxide ring may be opened in two ways as indicated by the arrows, and further that in each case the opening may or may not be accompanied by a Walden inversion. This leads to the theoretical possibility that four isomeric α-methylhexoside chlorohydrins may be formed and these are indexed as (VI*a*), (VI*b*), VI*c*), and (VI*d*). At the moment it is impossible to ascribe a definite configuration to either of our isomeric chlorohydrins and work on this problem continues. It is of interest to note, however, that each of them, on treatment with moist silver oxide, is converted into 2 : 3-anhydro-α-methylalloside (II). Moreover, the possibility that our compounds are oxonium salts may be discounted by the fact that on acetylation they give triacetyl α-methylhexoside chlorohydrins.

The problem of removing the benzylidene residue from 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside without interfering with the ethylene oxide ring was finally solved by using oxalic acid as the hydrolytic agent, and 2 : 3-anhydro-α-methylalloside (II) was obtained as a crystalline solid, m. p. 105—107°. The substance was then methylated with the Purdie reagents and 4 : 6-dimethyl 2 : 3-anhydro-α-methylalloside (III), m. p. 63—64, was obtained in almost quantitative yield. It proved to be identical with the 4 : 6-dimethyl 2 : 3-anhydro-α-methylhexoside obtained by the alkaline hydrolysis of 2 : 3-

di-*p*-toluenesulphonyl 4 : 6-dimethyl α-methylglucoside (Mathers and Robertson, J., 1933, 1080).

Now Robertson and Griffith (*loc. cit.*) have shown that, when 4 : 6-benzylidene 2 : 3-anhydro-α-methylalloside is treated with (a) aqueous caustic potash, and (b) sodium methoxide solution, the products are 4 : 6-benzylidene α-methylaltroside and 4 : 6-benzylidene 2-methyl α-methylaltroside respectively. Reasoning by analogy, treatment of 4 : 6-dimethyl 2 : 3-anhydro-α-methylalloside (III) with (a) aqueous caustic potash and (b) sodium methoxide solution should lead to the production of 4 : 6-*dimethyl α-methylaltroside* (IV) and 2 : 4 : 6-*trimethyl α-methylaltroside* (V) respectively. This proved to be the case.

When (III) was treated with aqueous caustic potash, 4 : 6-dimethyl α-methylaltroside (IV) was obtained in good yield as a very hygroscopic, crystalline substance. The presence of the altrose configuration was proved by methylation to give tetramethyl α-methylaltroside, which was identical with that obtained by Robertson and Griffith (*loc. cit.*). The altrosidic methyl group was removed from (IV) in the usual way by treatment with N-hydrochloric acid and 4 : 6-*dimethyl altrose* was obtained in fine needles, m. p. 158—160°, $[\alpha]_D^{15°}$ + 102·9° in water, changing to + 64·9° in six hours. The sugar yielded 4 : 6-*dimethyl altrosazone*, m. p. 139—141°, on treatment with phenylhydrazine in acetic acid solution.

In similar fashion treatment of (III) with sodium methoxide solution led to the production of 2 : 4 : 6-trimethyl α-methylaltroside (V), which was obtained as a hygroscopic syrup. Hydrolysis of this substance with N-hydrochloric acid yielded 2 : 4 : 6-*trimethyl altrose* as a pale yellow syrup, $[\alpha]_D^{15°}$ + 79·3° in chloroform. The position of the third methyl group was proved by the conversion of the sugar into 4 : 6-dimethyl altrosazone.

The hydrolysis of 4 : 6-dimethyl α-methylaltroside brings out a point of interest. Robertson and Griffith (*loc. cit.*) have shown that when α-methylaltroside, 2-methyl α-methylaltroside, 3-methyl α-methylaltroside, or 2 : 3-dimethyl α-methylaltroside is submitted to acid hydrolysis the reaction proceeds abnormally and leads to the production of a non-reducing anhydro-compound as the main product (cf. Richtmyer and Hudson, *J. Amer. Chem. Soc.*, 1935, **57**, 1716). Nothing definite could be said concerning the position of the anhydro-linkage in these compounds, but it was suggested that it must involve position 4 or 6. This suggestion is confirmed by the fact that 4 : 6-dimethyl α-methylaltroside is hydrolysed in normal fashion to give a reducing sugar which shows mutarotation.

EXPERIMENTAL.

Hydrolysis of 4 : 6-*Benzylidene* 2 : 3-*Anhydro-α-methylalloside with Hydrochloric Acid.*—The material (5 g.) was dissolved in a mixture of acetone (500 c.c.) and 2N-hydrochloric acid (18·5 c.c.) and boiled for 3 hours. After neutralisation with barium carbonate and filtration the acetone was distilled. The aqueous residue was washed with ether to remove benzaldehyde and then taken to dryness under diminished pressure. The dry residue was extracted with warm acetone; the acetone extract, on evaporation, yielded a syrup which, on rubbing with ether, gave 2·5 g. of a crystalline solid, m. p. 117—120°. This material contained chlorine and was shown to be a mixture of two isomeric α-methylhexoside chlorohydrins. The product was dissolved in the minimum amount of hot ethyl alcohol and a first fraction (A) was obtained; the mother-liquor was treated with light petroleum and a second fraction (B) was thus precipitated.

Fraction (A), m. p. 120—150°, was crystallised repeatedly from ethyl alcohol until the m. p. was constant and showed no change on crystallisation from acetone. In this way an *α-methylhexoside chlorohydrin*, m. p. 160—162°, $[\alpha]_D^{15°}$ + 113·1° in methyl alcohol (c = 1·265), was obtained in small prisms (Found: C, 39·8; H, 6·1; Cl, 16·9 $C_7H_{13}O_5Cl$ requires C, 39·5; H, 6·1; Cl, 16·7%).

Fraction (B), m. p. 120—130°, was crystallised repeatedly first from ethyl alcohol–light petroleum, then from acetone–ether, until the m. p. was constant and showed no change on crystallisation from ethyl acetate. In this way an isomeric *α-methylhexoside chlorohydrin*, m. p. 136—138°, $[\alpha]_D^{15°}$ + 157·2 in methyl alcohol (c = 1·646), was obtained in large prisms (Found: C, 39·6; H, 6·0; Cl, 17·0%).

Alkaline Hydrolysis of the Isomeric α-Methylhexoside Chlorohydrins.—The hydrolysis was carried out by means of freshly prepared silver oxide and in each case the product was 2 : 3-anhydro-α-methylalloside. A typical experiment is described. The substance (1 g.) was dissolved in water and boiled with an excess of freshly prepared silver oxide for 9 hours. The reaction liquid was filtered and taken to dryness under diminished pressure. The product was contaminated with colloidal silver, which was removed by extraction with methyl alcohol and filtration through norit. The gelatinous product thus obtained yielded, after several crystallisations from acetone, 2 : 3-anhydro-α-methylalloside, m. p. 105—107°, $[\alpha]_D^{15^\circ} + 153^\circ$ in methyl alcohol (cf. below).

Acetylation of the α-Methylhexoside Chlorohydrins.—The material (1·6 g.), a mixture of the isomers, was dissolved in dry pyridine (4 c.c.), and acetic anhydride (4 c.c.) added. After 15 hours, the reaction mixture was poured into water and extracted with benzene. The extract was washed with dilute acid, alkali, and water and dried over anhydrous sodium sulphate, and on removal of the solvent a syrup was obtained. This syrup contained chlorine and on analysis gave the figures required for a *triacetyl α-methylhexoside chlorohydrin* (Found : Cl, 10·5; 0·1158 g. of material required 13·75 c.c. of N/10-KOH. $C_{13}H_{19}O_8Cl$ requires Cl, 10·5%; 0·1158 g. requires 13·69 c.c. of N/10-KOH).

Partial Hydrolysis of 4 : 6-*Benzylidene* 2 : 3-*Anhydro-α-methylalloside.*—The material (5 g.), prepared as described by Robertson and Griffith (*loc. cit.*), was dissolved in acetone (450 c.c.) and after the addition of an aqueous solution of oxalic acid (15 g. in 50 c.c.) the mixture was boiled for 12 hours. After neutralisation with barium carbonate and filtration the acetone was distilled. At this point a small amount of unchanged starting material (0·5 g.) separated and was removed. The aqueous solution was washed with ether to remove benzaldehyde and evaporated to dryness under diminished pressure. The residue was extracted several times with acetone; the combined extracts, on evaporation, yielded a gelatinous product (2·7 g. or 90% yield). This material was purified with difficulty by repeated crystallisation from acetone and 2 : 3-*anhydro-α-methylalloside* was finally obtained as clusters of needles, m. p. 105—107°, $[\alpha]_D^{15^\circ} + 153^\circ$ in methyl alcohol ($c = 2{\cdot}058$) (Found : C, 48·3; H, 6·8; OMe, 17·0. $C_7H_{12}O_5$ requires C, 47·7; H, 6·8; OMe, 17·6%).

4 : 6-*Dimethyl* 2 : 3-*Anhydro-α-methylalloside.*—The above 2 : 3-anhydro-α-methylalloside was methylated six times with methyl iodide and silver oxide, and 4 : 6-dimethyl 2 : 3-anhydro-α-methylalloside was obtained in practically quantitative yield. The substance crystallised from light petroleum in long needles, m. p. 63—64°, $[\alpha]_D^{15^\circ} + 188{\cdot}0^\circ$ in chloroform ($c = 1{\cdot}475$), and proved to be identical with the 4 : 6-dimethyl 2 : 3-anhydro-α-methylhexoside obtained by Mathers and Robertson (*loc. cit.*), who record m. p. 63—64°, $[\alpha]_D + 188{\cdot}9^\circ$ in chloroform ($c = 1{\cdot}017$).

Action of Aqueous Caustic Potash on 4 : 6-*Dimethyl* 2 : 3-*Anhydro-α-methylalloside.*—A solution of the substance (5·8 g.) in 5% aqueous potassium hydroxide (225 c.c.) was heated on a steam-bath until the rotation was constant (20 hours) : $[\alpha]_D^{15^\circ} + 174{\cdot}6^\circ \longrightarrow + 133{\cdot}9^\circ$, allowing for change in concentration. The solution was saturated with potassium bicarbonate and extracted four times with chloroform; the combined extracts were dried over anhydrous sodium sulphate, filtered, and evaporated to dryness. The product was distilled, b. p. 130—135°/0·5 mm., and 4 : 6-*dimethyl α-methylaltroside* obtained as a syrup which crystallised on standing, $[\alpha]_D^{15^\circ} + 145{\cdot}7^\circ$ in chloroform ($c = 1{\cdot}38$). Yield, 4·1 g. The substance is exceedingly hygroscopic and the m. p. could not be determined with accuracy [Found : OMe, 40·35 (after drying at 100° in a vacuum for 8 hours). $C_9H_{18}O_6$ requires OMe, 41·9%].

Methylation of 4 : 6-*Dimethyl α-Methylaltroside.*—The substance required eight treatments with the Purdie reagents to effect complete methylation. 2 : 3 : 4 : 6-Tetramethyl α-methylaltroside was obtained in quantitative yield as a syrup, $n_D^{15^\circ}$ 1·4500, $[\alpha]_D^{15^\circ} + 128{\cdot}8^\circ$ in chloroform ($c = 1{\cdot}052$). Robertson and Griffith (*loc. cit.*) record $n_D^{15^\circ}$ 1·4500, $[\alpha]_D^{15^\circ} + 128{\cdot}3^\circ$ in chloroform ($c = 0{\cdot}931$) (Found : OMe, 59·9. Calc.: OMe, 62·0%).

Hydrolysis of 4 : 6-*Dimethyl α-Methylaltroside.*—The material (3·6 g.) was dissolved in N-hydrochloric acid (80 c.c.) and boiled in the presence of norit until the rotation was constant (3½ hours) : $[\alpha]_D^{15^\circ} + 139{\cdot}5^\circ \longrightarrow + 61{\cdot}7^\circ$, allowing for change in concentration. The solution was neutralised with barium carbonate, filtered, and taken to dryness under reduced pressure. The residue was extracted with chloroform, and the extract, after drying over anhydrous sodium sulphate, evaporated to dryness. The crystalline residue (2·1 g.) was recrystallised from acetone, and 4 : 6-*dimethyl altrose* obtained in fine needles, m. p. 158—160°, $[\alpha]_D^{15^\circ} + 102{\cdot}9^\circ$ in water ($c = 1{\cdot}96$), changing to $+ 64{\cdot}9^\circ$ after 6 hours (Found : OMe, 28·7. $C_8H_{16}O_6$ requires OMe, 29·8%).

Osazone of 4 : 6-*Dimethyl Altrose.*—The sugar (0·8 g.) was heated with a solution of phenylhydrazine (2 g.) in dilute acetic acid at 60° for 3 hours. The solid material which separated on cooling was contaminated with tarry matter, but after crystallisation, first from methyl alcohol and then from ethyl alcohol, 4 : 6-*dimethyl altrosazone* was obtained as a yellow crystalline solid, m. p. 139—141° (Found : OMe, 15·7. $C_{20}H_{26}O_4N_4$ requires OMe, 16·1%).

Action of Sodium Methoxide Solution on 4 : 6-*Dimethyl* 2 : 3-*Anhydro-α-methylalloside*.—The substance (5 g.) was dissolved in methyl alcohol (100 c.c.) containing sodium (2·7 g.), and the mixture boiled for 20 hours. After cooling and dilution with water, the reaction mixture was extracted four times with chloroform, and the united extracts, after drying over anhydrous sodium sulphate, were evaporated to dryness. The resulting syrup was distilled and 2 : 4 : 6-*trimethyl α-methylaltroside*, b. p. 105°/0·1 mm., $n_D^{15°}$ 1·4580, $[\alpha]_D^{15°}$ + 144·9° in chloroform (c = 1·984), was obtained as a very hygroscopic syrup. Yield, 4·3 g. or 80%. When it was left in contact with air for a short time, its refractive index fell from 1·4580 to 1·4550 (Found : OMe, 49·0. $C_{10}H_{20}O_6$ requires OMe, 52·5%).

Hydrolysis of 2 : 4 : 6-*Trimethyl α-Methylaltroside*.—The substance (2·05 g.) was dissolved in N-hydrochloric acid (40 c.c.) and boiled until the rotation became constant (3½ hrs.) : $[\alpha]_D^{15°}$ + 132° $\longrightarrow$ + 67·6°, allowing for change in concentration. The solution was neutralised with barium carbonate, filtered, and taken to dryness under diminished pressure. The residue was extracted with chloroform and the extract, after drying over anhydrous sodium sulphate, was evaporated. The resulting syrup was dissolved in ether, filtered, and again taken to dryness; 2 : 4 : 6-*trimethyl altrose* was then obtained as a pale yellow syrup, $n_D^{15°}$ 1·4765, $[\alpha]_D^{15}$ + 79·3° in chloroform (c = 1·617). Yield, 1·4 g. (Found : OMe, 40·1 after drying at 100° under reduced pressure for 8 hrs. $C_9H_{18}O_6$ requires OMe, 41·9%).

Osazone derived from 2 : 4 : 6-*Trimethyl Altrose*.—Treatment with phenylhydrazine acetate, as described in the case of 4 : 6-dimethyl altrose above, yielded a yellow crystalline substance, m. p. 139°, which proved to be 4 : 6-dimethyl altrosazone (m. p. and mixed m. p.).

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